Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation

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DOI:
10.1161/STROKEAHA.115.009487

Document Version
Peer reviewed version

Citation for published version (Harvard):
Senoo, K, Lip, GYH, Lane, DA, Büller, HR & Kotecha, D 2015, 'Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS Trial', *Stroke*, vol. 46, no. 9, pp. 2523-8. https://doi.org/10.1161/STROKEAHA.115.009487

Title: Residual risk of stroke and death in anticoagulated patients with permanent atrial fibrillation: the AMADEUS trial

Short title: Type of AF and adverse clinical outcomes

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Word count: Text – 2188; Abstract - 241

Tables: 4 & 1 supplementary Figures: 2

Keywords Atrial fibrillation, heart failure, stroke; mortality; permanent

Abstract

Background: Atrial fibrillation (AF) and heart failure frequently coexist and are associated with increased morbidity and mortality. We investigated the prognosis of anticoagulated patients with permanent AF and non-permanent AF according to pre-existing heart failure in the AMADEUS trial.

Methods: The primary outcome was a composite of cardiovascular death and stroke or systemic embolism (SSE), analysed using a Cox proportional hazards model, adjusted for baseline age, gender, diabetes, hypertension, creatinine and previous cardiovascular diseases. The median follow-up was 11.6 months (IQR 6.2-15.2).

Results: Non-permanent AF was present in 2072 patients (46% of cohort), of which 339 (16%) had pre-existing HF. 2484 patients had permanent AF (54% of cohort), with a higher burden of heart failure including 730 patients (29%); $p<0.001$. Overall, death due to cardiovascular causes occurred in 57 patients and 55 had SSE (1.4/100 person-years for each). Overall, the adjusted incidence of the composite outcome was higher in patients with permanent AF compared to non-permanent AF. In multivariate analysis, permanency of AF, creatinine, prior cerebrovascular events and previous coronary disease were independently associated with the primary outcome. The hazard ratio for permanent versus non-permanent AF was 1.68 (95% CI 1.08-2.55; $p=0.02$). The presence of heart failure attenuated the risk of adverse outcomes in a similar way in both permanent and non-permanent AF (interaction p-value=0.76).

Conclusion: The risk of cardiovascular death, stroke or systemic embolism is higher in anticoagulated patients with permanent compared to non-permanent AF, regardless of concomitant heart failure.

Introduction

Non-valvular atrial fibrillation (AF) increases the risk of stroke and systemic embolism (SSE), leading to substantial morbidity and mortality.[1] Whether the risk of stroke is affected by the type, duration, and frequency of AF has been debated for several years. Pooled analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) trials demonstrated a comparable risk of stroke in patients with paroxysmal and sustained AF treated with aspirin.[2 3, 4] In contrast, recently published data from the ROCKET-AF trial identified a higher rate of adverse outcomes in anticoagulated patients with persistent compared to paroxysmal AF, with borderline statistical significance for SSE (2.2 versus 1.7 per 100 patient-years; p=0.048) and significantly higher all-cause mortality (4.8 versus 3.5 per 100 patient-years; p=0.006).[5] Similar findings of increased stroke risk have been published from other studies using both vitamin K antagonists (VKA) and non-VKA oral anticoagulants (NOAC), including the SPORTIF and ARISTOTLE trials.[6, 7] Global surveys suggest that permanent AF is the most common type, accounting for around 50% of AF patients who also have a substantial burden of co-morbidities. This includes heart failure, present in 56% of patients with permanent AF, compared to 33% in paroxysmal and 44% in persistent AF.[8]

Practice guidelines on AF management address the prevention of SSE regardless of the type of AF, based on known risk factors in this patient population.[9, 10] The CHA_2DS_2-VASc score is a commonly-used risk prediction score for SSE, focusing on clinical risk factors.[11] The "C" criterion represents the higher stroke risk associated with recent decompensated heart failure irrespective of ejection fraction (thus including heart failure with reduced and preserved ejection fraction, as well as moderate-severe left ventricular systolic impairment on echocardiography).[12, 13] Moreover, the combination of AF and heart failure is associated with an increased risk of all-cause mortality and hospital admission, with numerous studies

suggesting that AF may be associated with progression of heart failure.[14-18] The impact of the type of AF on outcomes such as stroke and death in *anticoagulated* AF patients with and without heart failure remains controversial, particularly in regards to permanent compared to non-permanent AF. As both incidence and prevalence of AF are rapidly increasing[19], the burden of heart failure can be expected to rise proportionally. To investigate these aspects further, we reviewed data from the AMADEUS trial (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation), a multicentre, randomized, open-label study comparing fixed-dose idraparinux with dose-adjusted VKA therapy in AF patients with an indication for long-term anticoagulation.[20] We hypothesised that adverse outcomes would be more prevalent in permanent AF and aimed to assess the impact of heart failure in anticoagulated patients, accounting for the type of AF.

Methods

Study population

The design of the AMADEUS trial has previously been described.[20, 21] In brief, the AMADEUS trial was a multicentre, randomized, open-label non-inferiority study with blinded assessment of outcome that compared fixed-dose idraparinux with conventional anticoagulation by dose-adjusted oral VKA therapy for the prevention of thromboembolism in patients with AF. Eligible patients had ECG-documented non-valvular AF and an indication for long-term anticoagulation, based on the presence of at least one of the following risk factors: previous ischemic stroke, transient ischemic attack (TIA) or systemic embolism, hypertension requiring drug treatment, left ventricular dysfunction, age >75 years, or age 65-75 with either diabetes mellitus or symptomatic coronary artery disease (CAD). Exclusion criteria included the inability to provide consent, contraindication or other requirement for anticoagulation, calculated creatinine clearance of <10 mL/min, breastfeeding, pregnancy and recent or anticipated invasive procedures with potential for uncontrolled bleeding. We examined the population according to type of AF, considering non-permanent AF (comprising paroxysmal and persistent) versus permanent AF. The presence of investigator-documented heart failure at baseline was used to sub-categorise the population.

Definitions of endpoint

This post-hoc analysis of the AMADEUS trial used pooled data from both the VKA and idraparinux arms on an intention to treat basis. The primary outcome of this analysis was the composite of cardiovascular (CV) death and SSE. Stroke included ischaemic, haemorrhagic or undefined causes that resulted in a focal neurological deficit of sudden onset, with a corresponding defect on brain imaging. Systemic embolism was confirmed by angiography,

surgery, or autopsy. The safety outcome of the present analysis was major bleeding in the VKA arm of the trial, defined as bleeding that was fatal, intracranial or affecting another critical anatomical site, overt bleeding with a drop of haemoglobin ≥20 g/L or requiring transfusion of two or more units of erythrocytes. All suspected outcome events were classified by the original AMADEUS central adjudication committee who were blinded to treatment assignment.

Statistical analysis

The characteristics of the patients are reported as percentages and mean ± standard deviation (SD). Comparisons between patients with and without pre-existing heart failure were made using Fisher's exact test when comparing categorical variables and t-tests or the Mann–Whitney U-test, as appropriate for continuous variables. Outcomes by type of AF (permanent AF versus non-permanent) were calculated by the overall rate of adverse events per 100 patient-years after adjustment for age and sex. A Cox proportional hazard model was used to identify the independent characteristics associated with outcomes during follow-up. The multivariate model included adjustment for age, sex, creatinine (log-transformed), hypertension, diabetes mellitus and previous stroke/TIA/thromboembolism and CAD. The results are expressed as hazard ratios (HR) and 95% confidence intervals (CI). Schoenfeld residuals were used to confirm proportional hazards over time. All interactions were evaluated in the multivariate Cox model, including two post-hoc defined exploratory analyses according to treatment allocation and time in therapeutic range (TTR) for those randomised to VKA. The adjusted probabilities comparing permanent and non-permanent AF were analysed using an adjusted logistic regression model, with heart failure interaction determined using a likelihood ratio test. Kaplan–Meier curves were assessed using a log-rank test. A two-tailed p-value <0.05 was considered statistically significant. Analyses were performed using SPSS (version 21) and Stata (version 13.1).

Results

Atrial fibrillation was present in 4556 patients. Non-permanent AF accounted for 2072 patients (46% of cohort), of which 339 (16%) had pre-existing heart failure. Permanent AF was documented in 2484 patients (54% of cohort), with a higher burden of heart failure that included 730 patients (29%); $p<0.001$ compared to non-permanent AF. Baseline characteristics according to type of AF are presented in Table 1. Patients with permanent AF were older, with more men, a higher rate of diabetes, less hypertension and overall a marginally higher CHA_2DS_2-VASc score. Patients with pre-existing heart failure had a higher frequency of men, diabetes, renal impairment and CAD than those without a history of heart failure (see Supplementary Table).

Table 2 presents the outcomes observed over a median follow-up of 11.6 months (interquartile range [IQR] 6.2 to 15.2). The primary composite outcome occurred in 68 patients in permanent AF (3.0/100person-years) and 31 patients in non-permanent AF (1.7/100 person-years). There were numerically more outcomes among those with permanent AF for each component of the primary outcome (CV death and SSE; see Table 2) but these differences were not significant. The hazard ratio for the primary outcome comparing permanent versus non-permanent AF was 1.73 in univariate analysis (95% CI 1.13-2.64; p=0.01) and 1.66 following multivariate adjustment (95% CI 1.08-2.55; p=0.02); see Table 3. The Kaplan-Meier event curves are depicted in Figure 1 (log-rank p=0.01). Other variables independently associated with the primary outcome were creatinine, prior cerebrovascular events and previous CAD. In exploratory analyses, neither allocation to treatment arm (VKA or Idraparinux) nor TTR in VKA patients interacted with the association of AF type and the primary outcome (p=0.19 and 0.38 respectively).

Due to the low number of events, we were limited in power to detect differences between permanent and non-permanent AF in the sub-groups with and without heart failure. However, the same trend of an increase in adverse events in those with permanent AF compared to non-permanent AF was evident, regardless of heart failure status (see Table 2). The interaction p-value between AF type and heart failure status for the primary outcome was 0.76. Figure 2 displays the adjusted probabilities of the primary outcome according to the four sub-groups, demonstrating a similar increase in adverse events with concomitant heart failure in both permanent and non-permanent AF.

Bleeding outcomes in the warfarin arm of the trial are listed in Table 4. Major bleeding, and a composite with CV death and SSE, were not significantly different between patients with permanent and non-permanent AF, irrespective of the presence of heart failure.

Discussion

Our analysis demonstrates that in anticoagulated patients, permanent AF is associated with a higher risk of the composite endpoint of CV death, stroke or systemic embolism compared to non-permanent forms of AF. This finding was maintained even after adjustment for potential confounders that could influence the risk of events. Importantly, we did not identify any interaction with pre-existing heart failure, confirming that the adverse risk associated with permanent AF is independent of heart failure status.

Atrial fibrillation results in a considerable burden on patients and healthcare systems, leading to an increased risk of stroke, hospital admission and death.[22] Permanent AF is the most common form and is associated with numerous other cardiovascular risk factors.[8] The impact of AF, particularly in regard to type of AF, has previously been difficult to define due to variation in the use of anticoagulation, differences in comorbidities and the presence of heart failure. Concomitant AF and heart failure are common in clinical practice and regardless of which comes first, patients have a much poorer prognosis. The Framingham study showed that in AF patients, heart failure was associated with significantly increased mortality (HR 2.7 in men [95% CI 1.9-3.7] and 3.1 in women [95% CI 2.2-4.2]).[16] In a meta-analysis of heart failure patients, the presence of AF was associated with higher risk of death both in randomized trials and observational studies (odds ratio 1.40, 95% CI 1.32-1.48 and 1.14, 95% CI 1.03-1.26, respectively).[23]

Activation of the renin-angiotensin system and chronic atrial stretch due to structural heart disease can lead to histological changes in the atria.[24, 25] Subsequently, this atrial remodelling is more likely to be associated with longer AF episodes and other complications.[26, 27] Indeed,

Taillandier *et al* found that permanent AF in patients with heart failure is associated with a higher risk of death and hospitalization for heart failure, mostly in patients with preserved left ventricular ejection fraction.[28] These results suggested that the duration of AF episodes might be a potential risk factor for adverse outcomes in patients with heart failure, in addition to comorbidities and hemodynamic status.

In general, the duration of AF episodes leading to thrombus formation are poorly known, and therefore clinicians have usually been less likely to treat short and infrequent episodes of AF with oral anticoagulation than patients with persistent or permanent AF.[29 30] In the Stockholm Cohort Study on Atrial Fibrillation, ischemic strokes were twice as common in paroxysmal AF than predicted in the general population, but the same in paroxysmal AF and permanent AF.[31] Of note, anticoagulation with VKA was only prescribed at baseline in 28% and 49%, respectively, and none of these analyses included consistently anticoagulated patients. In contrast, we were able to study the residual risk of adverse outcomes in anticoagulated patients. Following consistent anticoagulation with either dose-adjusted warfarin or fixed-dose idraparinux, our data demonstrate that permanent AF was associated with worse outcomes. Similarly, in sub-studies of recent randomised trials on non-VKA anticoagulants, patients with persistent or permanent AF had a significantly higher rate of thromboembolic events compared to those with paroxysmal AF.[5, 7]

Heart failure attenuated the risk of adverse outcomes similarly in both permanent and non-permanent AF patients. In patients with AF, hearty failure has been strongly associated with SSE and mortality, and independently adds to risk prediction.[13 32] However, the mechanisms underlying this association remain an area of ongoing research. Future studies of heart failure and AF should consider these aspects to improve our understanding of their complex inter-relationship.[18] Our findings suggest that regardless of other comorbidities such as heart

failure, patients with permanent AF have considerable risk of residual morbidity and mortality, even after anticoagulation. This finding has important implications for AF treatment strategies and necessitates on-going management and the identification of where residual risks can be reduced further after anticoagulation.

Limitations

These results are based on a post-hoc analysis of the AMADEUS trial, and should be interpreted as hypothesis-generating. The AMADEUS population was at relatively low risk of both ischemic stroke and bleeding events compared with "real-world" patients, with limited statistical power for sub-group comparisons. We accepted the definition of heart failure as defined in the AMADEUS trial but were unable to delineate those patients with reduced or preserved ejection fraction. Nevertheless, stroke outcomes in AF patients do not appear to differ according to ejection fraction.[12, 33] Data regarding heart failure therapies were also not available, which may have affected outcomes differently according to type of AF.

Conclusion

This post-hoc analysis of the AMADEUS trial confirms a significantly higher risk of cardiovascular death, stroke or systemic embolism in anticoagulated patients with permanent AF compared to non-permanent AF. Concomitant heart failure attenuates the residual risk of adverse outcomes after anticoagulation similarly in both permanent and non-permanent AF.

Conflict of interest

Keitaro Senoo: No conflicts.

Deirdre A Lane: Investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim. Speaker's bureau for Boehringer Ingelheim, Bristol-Myers-Squibb and Bayer for lectures at educational meetings. Dr Lane is also on the Steering Committee of a Phase IV clinical trial sponsored by Bristol-Myers-Squibb.

Harry R Büller: Consulting fees from the sponsor for activities involved in the design and supervision of the study and the analysis and reporting of results.

Gregory YH Lip: Consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, Daiichi-Sankyo, Medtronic and Boehringer Ingelheim. Speaker's bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

Dipak Kotecha: Research funding and honoraria from Menarini, professional development support from Daiichi-Sankyo and is the lead for the Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF).

Funding:

Sanofi SA provided the study dataset. The analysis of the dataset was conducted fully independent of any industry or other grant support.

KS is a grantee of NIHON KOHDEN/ St.Jude Medical Arrhythmia Fellowship.

Table 1: Baseline characteristics according to type of AF

	Non-Permanent AF	Permanent AF	P value
Number	2072	2484	
Age, years ± SD	69.0 ± 9.3	71.1 ± 8.7	<0.001
Age >75 (%)	30.4	39.2	<0.001
Gender, male (%)	62.4	69.9	<0.001
Hypertension (%)	80.2	74.5	<0.001
Diabetes mellitus (%)	18.0	20.9	0.01
Previous stroke, TIA or TE (%)	24.4	23.4	0.44
Coronary artery disease (%)	30.3	31.2	0.48
Creatinine clearance ± SD	77.3 ± 30.5	75.8 ± 31.3	0.12
>80 ml/min (%)	38.6	37.7	
50-80 ml/min (%)	43.8	43.4	
30-49 ml/min (%)	15.4	17.2	
<30 ml/min (%)	1.5	1.4	
Concurrent treatment			
Aspirin (%)	17.9	15.0	0.01
Clopidogrel or ticagrelor (%)	1.9	1.1	0.04
TTR in warfarin arm ± SD	0.56 ± 0.20	0.58 ± 0.20	0.002
CHA_2DS_2-VASC score			
Mean ± SD	3.3 ± 1.5	3.5 ± 1.5	<0.001
By category:			<0.001
Score of 0 in men or 1 in women (%)	0	0	
Score of 1 in men (%)	10.8	7.4	
Score of 2 or more (%)	89.2	92.6	

TIA, transient ischemic attack; TE, thromboembolism; AF, atrial fibrillation; TTR, time in therapeutic range.

Table 2: Outcomes according to type of AF at baseline

	Non-permanent AF No. of events (/100 patient-years)	Permanent AF No. of events (/100 patient-years)	Adjusted hazard ratio (95% CI)*	p-value
Whole group				
Number	2072	2484		
Combined CV death and SSE	31 (1.7)	68 (3.0)	1.59 (1.04-2.44)	0.03
CV death	18 (1.0)	39 (1.7)	1.52 (0.86-2.66)	0.15
SSE	16 (0.9)	29 (1.3)	1.38 (0.74-2.55)	0.31
With pre-existing heart failure				
Number	339	730		
Combined CV death and SSE	8 (2.6)	24 (3.6)	1.28 (0.57-2.86)	0.55
CV death	6 (2.0)	18 (2.7)	1.30 (0.51-3.28)	0.58
SSE	4 (1.3)	6 (0.9)	0.66 (0.18-2.33)	0.51
Without heart failure				
Number	1733	1754		
Combined CV death and SSE	23 (1.6)	44 (2.8)	1.62 (0.97-2.69)	0.06
CV death	12 (0.8)	21 (1.3)	1.38 (0.68-2.83)	0.37
SSE	12 (0.8)	23 (1.4)	1.71 (0.85-3.46)	0.13

CV, cardiovascular; SSE, stroke and systemic embolus.

Table 3: Cox regression analysis for the primary composite outcome regardless of heart failure status

	Univariate		**Multivariate**	
Risk factor	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Permanent versus non-permanent AF	1.73 (1.13-2.64)	0.01	1.66 (1.08-2.55)	0.02
Creatinine	0.27 (0.17-0.43)	<0.001	0.35 (0.19-0.66	0.001
Prior stroke/TIA/TE	2.14 (1.43-3.20)	<0.001	1.97 (1.31-2.96)	0.001
Coronary artery disease	1.94 (1.31-2.88)	0.001	1.72 (1.14-2.57)	0.009
Age	1.06(1.03-1.10)	0.001	1.02 (0.99-1.05)	0.31
Sex	1.22(0.75-1.98)	0.42	1.26 (0.81-1.95)	0.31
Hypertension	0.98 (0.62-1.55)	0.92	1.23 (0.77-1.97)	0.38
Diabetes mellitus	1.04 (0.64-1.71)	0.86	0.97 (0.59-1.59)	0.90

TIA, transient ischemic attack; TE, thromboembolism.

Table 4: Bleeding outcomes in the warfarin arm

	With pre-existing heart failure (n=541)			Without heart failure (n=1744)		
	Non-permanent AF No. of events (%/100 patient-years)	Permanent AF No. of events (%/100 patient-years)	Unadjusted p-value	Non-permanent AF No. of events (%/100 patient-years)	Permanent AF No. of events (%/100 patient-years)	Unadjusted p-value
Number	166	375		861	883	
Major bleeding	2 (1.3)	6 (1.7)	1.00	8 (1.1)	13 (1.6)	0.38
Composite of major bleeding, CV death or SSE	7 (4.5)	19 (5.3)	0.83	23 (3.0)	32 (3.9)	0.28

CV, cardiovascular; SSE, stroke and systemic embolus.

Supplementary Table: Baseline characteristics according to heart failure status

	No prior heart failure	Pre-existing heart failure	P value
Number	3487	1069	
Gender, male (%)	63.3	76.9	<0.001
Age, years ± SD	70.3 ± 8.9	69.5 ± 9.6	0.01
Age >75 (%)	35.7	33.4	0.16
Hypertension (%)	80.6	65.6	<0.001
Diabetes mellitus (%)	18.4	23.5	<0.001
Previous stroke, TIA or TE (%)	25.4	18.6	<0.001
Coronary artery disease (%)	26.4	45.0	<0.001
Creatinine clearance ± SD	77.1 ± 30.9	74.5 ± 31.1	0.003
>80 ml/min (%)	38.7	36.3	<0.001
50-80 ml/min (%)	44.3	41.2	
30-49 ml/min (%)	15.3	20.0	
<30 ml/min (%)	1.2	2.3	
Type of AF			<0.001
Permanent AF (%)	50.3	68.3	
Non-permanent AF (%)	49.7	31.7	
Concurrent treatment			
Aspirin (%)	15.2	19.9	<0.001
Clopidogrel or ticagrelor (%)	1.4	1.7	0.56
TTR in warfarin arm ± SD	0.58 ± 0.20	0.56 ± 0.22	0.07
CHA_2DS_2-VASC score			
Mean ± SD	3.3 ± 1.5	4.0 ± 1.6	<0.001

TIA, transient ischemic attack; TE, thromboembolism.

Figure legends

Figure 1:

Kaplan Meier event curves for cardiovascular death, stroke or systemic embolism by type of AF

Figure 2:

Adjusted probabilities for cardiovascular death, stroke or systemic embolism according to type of AF and heart failure status

Figure 1

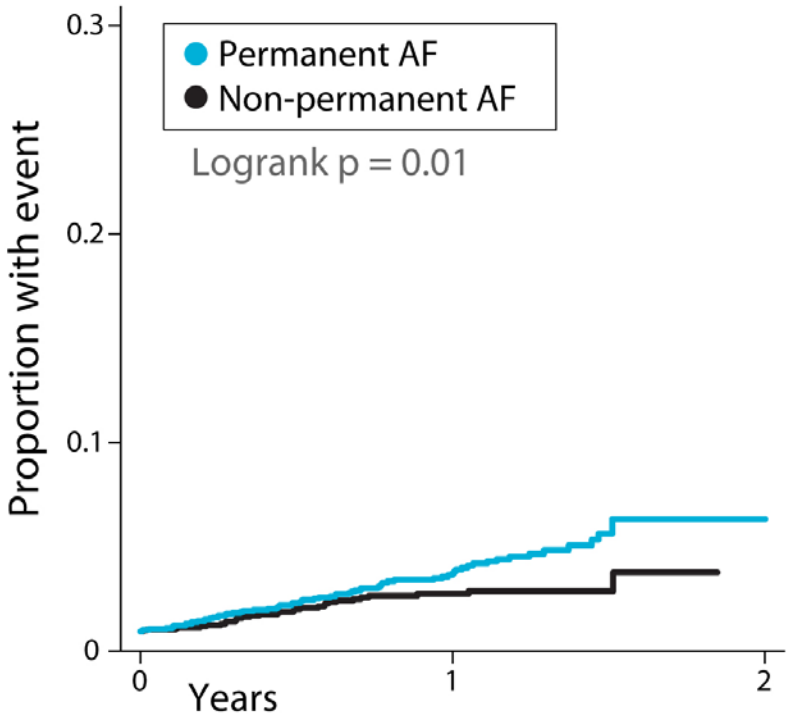
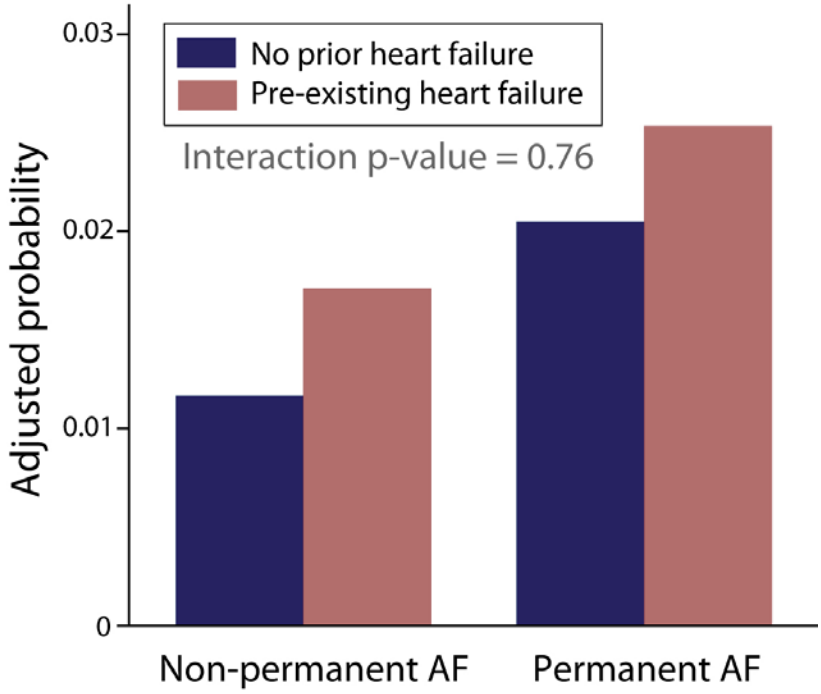

Permanent AF
Non-permanent AF
Logrank p = 0.01
Proportion with event
0.3
0.2
0.1
0
0
1
2
Years

Figure 2


0.03
0.02
0.01
0
Adjusted probability
No prior heart failure
Pre-existing heart failure
Interaction p-value = 0.76
Non-permanent AF
Permanent AF

References

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369-2429

2. Aboaf AP, Wolf PS. Paroxysmal atrial fibrillation. A common but neglected entity. *Arch Intern Med*. 1996;156:362-367

3. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke*. 1986;17:622-626

4. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol*. 2000;35:183-187

5. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J*. 2015;36:288-296

6. Lip GY, Frison L, Grind M. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *J Intern Med*. 2008;264:50-61

7. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J*. 2013;34:2464-2471

8. Chiang CE, Naditch-Brule L, Murin J, Goethals M, Inoue H, O'Neill J, Silva-Cardoso J, Zharinov O, Gamra H, Alam S, Ponikowski P, Lewalter T, Rosenqvist M, Steg PG. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythm Electrophysiol*. 2012;5:632-639

9. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blomstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbuchel H, Heldal M, Kristensen SD, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FW. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719-2747

10. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huezey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS, Smith SC, Jr., Priori SG, Estes NA, 3rd, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Jacobs AK, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson WG, Tarkington LG, Yancy CW. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011;123:e269-367

11. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272

12. Kotecha D, Banerjee A, Lip GY. Increased stroke risk in atrial fibrillation patients with heart failure: does ejection fraction matter? *Stroke*. 2015;46:608-609

13. Agarwal M, Apostolakis S, Lane DA, Lip GY. The impact of heart failure and left ventricular dysfunction in predicting stroke, thromboembolism, and mortality in atrial fibrillation patients: a systematic review. *Clin Ther*. 2014;36:1135-1144

14. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JGF, Lip GYH, Coats AJS, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384:2235-2243

15. Dries D, Exner D, Gersh B, Domanski M, Waclawiw M, Stevenson L. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *J Am Coll Cardiol*. 1998;32:695-703

16. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal Relations of Atrial Fibrillation and Congestive Heart Failure and Their Joint Influence on Mortality: The Framingham Heart Study. *Circulation*. 2003;107:2920-2925

17. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol*. 1998;32:695-703

18. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol*. 2006;47:1997-2004

19. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of Current and Future Incidence and Prevalence of Atrial Fibrillation in the U.S. Adult Population. *Am J Cardiol*. 2013;112:1142-1147

20. AMADEUS Investigators, Bousser MG, Bouthier J, Buller HR, Cohen AT, Crijns H, Davidson BL, Halperin J, Hankey G, Levy S, Pengo V, Prandoni P, Prins MH, Tomkowski W, Torp-Pedersen C, Wyse DG. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet*. 2008;371:315-321

21. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. *J Am Coll Cardiol*. 2012;60:861-867

22. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol*. 2014;6:213-220

23. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail*. 2009;11:676-683

24. Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. *Circulation*. 1992;85:1046-1055

25. Ohkusa T, Ueyama T, Yamada J, Yano M, Fujumura Y, Esato K, Matsuzaki M. Alterations in cardiac sarcoplasmic reticulum Ca2+ regulatory proteins in the atrial tissue of patients with chronic atrial fibrillation. *J Am Coll Cardiol*. 1999;34:255-263

26. Solti F, Vecsey T, Kekesi V, Juhasz-Nagy A. The effect of atrial dilatation on the genesis of atrial arrhythmias. *Cardiovasc Res*. 1989;23:882-886

27. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev*. 2011;91:265-325

28. Taillandier S, Brunet Bernard A, Lallemand B, Simeon E, Pericart L, Clementy N, Babuty D, Fauchier L. Prognosis in patients hospitalized with permanent and nonpermanent atrial fibrillation in heart failure. *Am J Cardiol*. 2014;113:1189-1195

29. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J*. 2005;26:2422-2434

30. Waldo AL, Becker RC, Tapson VF, Colgan KJ. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol*. 2005;46:1729-1736

31. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J*. 2010;31:967-975

32. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272

33. Sandhu RK, Hohnloser SH, Pfeffer MA, Yuan F, Hart RG, Yusuf S, Connolly SJ, McAlister FA, Healey JS. Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. *Stroke*. 2015;46:667-672